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L3: Entry 69 of 116 File: USPT Mar 9, 1999

DOCUMENT-IDENTIFIER: US 5879703 A
** See image for Certificate of Correction **
TITLE: Encapsulation of active ingredients into lipid vesicles

Brief Summary Text (7):
U.S. Pat. No. 5,100,662 issued to Bolcsak et al. on Mar. 31, 1992 describes liposomes or liposome-like structures comprising sterols either alone or in combination with additional liposome-forming lipids. Liposome structures such as micelles, reverse micelles, hexagonal phases, multilamellar vesicles, or unilamellar vesicles are described. The liposomes may be prepared with or without the use of an organic solvent and may function as vaccines after entrapment or association of an immunogen.

Brief Summary Text (9):
U.S. Pat. No. 4,900,549 issued to de Vries on Feb. 13, 1990, relates to a process for preparing immunogenic complexes. The patent describes an amphipathic antigenic protein or peptide contacted with a solution containing a detergent, a sterol, and a glycoside comprising hydrophobic and hydrophilic regions. Subsequently, the detergent is removed and the immunogenic complex is purified. Optionally, the solution further comprises a phospholipid, preferably phosphatidylethanolamine. The structure is described as consisting of cage-like or two-dimensional aggregates, depending upon whether phospholipid is or is not present, respectively.

Detailed Description Text (3):
Specifically, an SDMC precursor solution is first prepared. The precursor solution is prepared by solubilizing a phospholipid material containing the following phosphatides: phosphatidylcholine, phosphatidylethanolamine, phosphatidic acid and phosphatidylinositol at an approximate ratio of 6.5:2.5:0.7:0.3 in ethanol, one gram of the phospholipid material to between about 5.0-7.5 mls of the ethanol solvent. The phosphatides, preferably, can consist of purified soybean phosphatides and were supplied by American Lecithin Company of New York, N.Y. Water is then added to the phospholipid/solvent mixture to form a turbid suspension. A second quantity of solvent, in this instance ethanol, is added to the turbid suspension until the suspension turns clear. An SDMC precursor solution result which is characterized by having optical clarity at room temperature and being monophasic at room temperature.

Current US Original Classification (1):
424/450

L3: Entry 73 of 116 File: USPT Nov 10, 1998

DOCUMENT-IDENTIFIER: US 5834012 A
** See image for Certificate of Correction **
TITLE: Lipid complexed topoisomerase I inhibitors

Brief Summary Text (15):
The present invention concerns lipid/drug complexes comprising an inhibitor of topoisomerase I of the camptothecin class and phospholipids with unsaturated fatty acids. The presence of unsaturated fatty acids appears to be important to achieve a good complexation with camptothecin Family members. The complexes may be micellar particles or liposomes depending on the lipids used. In order to unify the nomenclature the general term micelle will be used to refer to both micelles and inverted micelles. The general term liposome will be used to describe the incorporation of the drug in a spherical (or vesicular) structure (visualized by fluorescent microscopy). The term liposome will be used to describe both unilamellar and multilamellar liposomes.

Brief Summary Text (18):
The lipid component of the LC-TII is composed of any number of different lipids (either alone or in combination). Preferred lipids are phospholipids with one or two mono or poly-unsaturated fatty acids, such as oleic (18:1), linoleic (18:2), linoleoleic (18:3), eicosenoic (20:1), myristoleic (14:1), palmitoleic (16:1), etc., and different neutral, positively charged, and negatively charged polar head groups such as choline, ethanolamine, glycerol, or serine, with or without different covalent associated moieties (covalent association phospholipids). For example, the lipid may be: dioleoyl phosphatidylglycerol (DOPG), dioleoyl phosphatidylcholine (DOPC), or dioleoyl phosphatidylserine (DOPS). Cationic lipids, such as phosphatidylethanolamine (DOPE), (DOTMA), dioleoyl 1-3-dioleoyl Trimethylammonium-propane (DOTAP), stearylamine etc. can also be used. Particularly preferred phospholipids contain the fatty acid chain oleic (18:1 -this denotes that the fatty acid chain contains 18 carbons and 1 unsaturated double bond). When oleic acid is covalently bound to a head group, it is termed "oleoyl". The addition of cationic lipids such as DOTAP and stearylamine can be used to enhance lipid complexation with CPT. PEG-phospholipids can be added to prolong the half life of the lipid/drug complexes. Cholesterol can also be incorporated to enhance the stability of the complexes. Further preferred embodiments comprise the covalent associate phospholipids described below.

Brief Summary Text (19):
One contemplated formulation is comprised of CPT and a covalent association phospholipid (CA lipid), i.e., dioleoyl-N-glutaryl-phosphatidyl ethanolamine (DO-NGPE). CA lipids are typically used to covalently associate ligands such as proteins with the exterior surface of liposomes. These lipids have not heretofore been employed as a major structural component of a lipid drug micellar complex. Examples of commercially available covalent association phospholipids are N-PDP-phosphatidylethanolamine, N-succinyl-phosphatidylethanolamine, N-glutaryl-phosphatidylethamolamine, N-dodecanyl-phosphatidylethanolamine and N-biotinyl-phosphatidylethanolamine. NGPE has been found to be a particularly preferred lipid. NGPE has two negative charges, and it is anticipated that other lipids having two negative charges will have advantages similar to NGPE. A CA lipid may be present as the only lipid in an LC-TII, or as one of two or more lipid components of LC-TII.

For example, a CA lipid may form from 1%-100% of the lipid portion of an LC-TII. Preferably, the CA lipid will be in the range of 25%-100% of the lipid portion, with all percentages between these points being possible.

Brief Summary Text (32):
Certain compositions may be particularly distinct and advantageous when the target cell, its localization, or the amount of drug delivered is important. Alternatively the topoisomerase I inhibitor may be mixed with other agents including other lipids to form a heterogenous micellar-liposome suspension, a micelle in liposome suspension, or a pure liposome suspension. These agents might include stabilizers, e.g. buffers, surfactants other lipids or combinations of lipids, other therapeutic agents, and the like.

Brief Summary Text (34):
The liposome drug or micellar-drug complex may be introduced into contact with cells by a variety of methods. As used herein the terms "contact", "contacted", and "contacting", are used to describe the process by which an effective amount of a topoisomerase I inhibitor, e.g., CPT, comes in direct juxtaposition with the target cell. In cell culture, the micelles can simply be dispersed in the cell culture solution. The topoisomerase I inhibitor-lipid complex can be introduced into a cancer cell by preparing a topoisomerase-inhibitor/lipid complex; and contacting or treating cancer cells with a pharmacologically effective amount of the topoisomerase-inhibitor/lipid complex.

Current US Original Classification (1):
424/450

Other Reference Publication (16):
Stamatatos etal., "Interactions of Cationic Lipid Vesicles with Negatively Charged Phospholipid Vesicles and Biological Membranes," Biochemistry, 27:3917-3925, 1988.

CLAIMS:

1. A complex comprising a topoisomerase I inhibitor complexed to a phospholipid, the phospholipid comprising two fatty acids attached to a head group, wherein at least one of the fatty acids is an oleic acid.

2. The complex of claim 1, wherein the phospholipid DO-
NGPE,DOPG,DOPE,DOPC,DOTMA,DOTAP, or DOPS.

3. The complex of claim 1, wherein the composition is further defined as comprising two phospholipids, each phospholipid comprising two fatty acids attached to a head group wherein at least of the fatty acids in each phospholipid is an oleic acid.

4. The complex of claim 1, further defined as comprising three phospholipids, each phospholipid two fatty acids attached to a head group, wherein at least one of the fatty acids in each phospholipid is an acid.

5. The complex of claim 4 wherein the three phospholipids are DOPE, DOPC, and DOTAP.

7. The complex of claim 1, further comprising a positively charged phospholipid.

8. The complex of claim 1, wherein the positively charged phospholipid is DOTAP or stearylamine.

19. A pharmaceutical composition comprising a pharmaceutically effective amount of an LC-TII comprising a topoisomerase I inhibitor complexed to a phospholipid, the phospholipid comprising two fatty acids attached to a head group, wherein at least one of the fatty acids is an oleic acid wherein the LC-TII is in a pharmaceutically

acceptable carrier.

20. The pharmaceutical composition of claim 19, wherein the phospholipid comprising the oleic fatty acid is DOPG, DOPE, DOPC, DOTMA, DOTAP, or DOPS.

21. The pharmaceutical composition of claim 19, comprising the phospholipids DOPE, DOPC, and DOTAP.

22. The pharmaceutical composition of claim 19, comprising a positively charged phospholipid.

23. The pharmaceutical composition of claim 22, wherein the positively charged phospholipid is DOTAP or stearylamine.

25. A phospholipid-topoisomerase I inhibitor complex comprising a topoisomerase I inhibitor complexed to a phospholipid comprising two fatty acids attached to a head group, wherein at least one of the fatty acids is an oleic acid, the phospholipid selected from the group consisting of DO-NGPE,DOPG,DOPE, DOPC,DOTMA,DOTAP and DOPS.

26. The complex of claim 25, wherein the complex is further defined as comprising two phospholipids, each phospholipid comprising two fatty acids attached to a head group, wherein at least one of the fatty acids in each phospholipid is an oleic acid.

27. The complex of claim 26, further defined as comprising three phospholipids, each phospholipid comprising two fatty acids attached to a head group, wherein at least one of the fatty acids in each phospholipid is an oleic acid.

28. The complex of claim 27, wherein the three phospholipids are DOPE, DOPC, and DOTAP.

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L3: Entry 87 of 116 File: USPT Jan 14, 1997

DOCUMENT-IDENTIFIER: US 5593687 A
TITLE: Aqueous dispersion containing liposomes

Brief Summary Text (3):
The process of this invention is suitable for the production of dispersions such as, for example, aqueous suspensions, aqueous emulsions, e.g., o/w emulsions and o/w/o emulsions, and aqueous formulations containing liposomes, micelles, colloids, etc.

Brief Summary Text (9):
Aqueous phases containing liposomes or micelles are frequently produced by dissolving the liposome- or micelle-forming compounds and, if desired, also the active ingredients (e.g., medicinal agents) in a solvent, introducing the solution into the aqueous phase, the latter also optionally containing active ingredients, and, if desired after homogenization, removing the solvent by distillation ("Pharmazie in unserer Zeit" [Pharmacy in Our times] 11: 97-108, 1982; Pure and Appl. Chem. 53: 2241-2254, 1981; DE-A 2,730,570).

Brief Summary Text (10):
Surprisingly, if, in the preparation of such dispersions, the liquid to be removed is removed by membrane distillation, rather than by simple distillation, the particle sizes of the resultant dispersion can be freely selected within wide limits. Also, the dispersions exhibit a significantly more uniform particle distribution. Moreover, the process of this invention has the advantage, especially when preparing phase mixtures containing liposomes or micelles, that it can be performed on an industrial scale substantially more simply than, for example, the REV process (see U.S. Pat. No. 4,235,871). As is known, the REV process is of little suitability for industrial production of such dispersions.

Brief Summary Text (33):
The process of this invention offers special advantages in the manufacture, on an industrial scale, of phase mixtures which contain liposomes or micelles since these mixtures, as mentioned above, can be manufactured in relatively large quantities only with difficulty by means of the previously known methods.

Brief Summary Text (34):
Phase mixtures containing liposomes or micelles are, as is known, of significance, inter alia, for the encapsulation or solubilizing of active compounds. According to the invention, they are prepared by dissolving the compounds forming liposomes and/or micelles, and optionally also the active ingredient(s), in a volatile organic solvent (e.g., ethanol, ethyl acetate, diethyl ether), introducing the solution into the aqueous phase, the latter also optionally containing the active compound(s), if desired, and removing the solvent by transmembrane distillation or pervaporation.

Brief Summary Text (38):
Suitable lipids include, for example, monoglycerides, sulfatides and, in particular, phospholipids, such as the sphingomyelins, the plasmalogens, the phosphatidylcholines, the phosphatidylethanolamines, the phosphatidylserines, the phosphatidylinositols, and the cardiolipins, as well as mixtures of these lipids

(Dr. Otto-Albert Neumuller: Rompps Chemie-Lexikon; Franckh'sche Verlagshandlung, Stuttgart [Germany] 2665; 3159; 3920; and 4045).

Brief Summary Text (47):
For preparing liposome-containing, aqueous phase mixtures, the aforementioned phospholipids and mixtures of these phospholipids with cholesterol and/or charge carriers, e.g., stearylamine, stearic acid or diacetyl phosphate are preferably utilized. In this case, preferably about 0.1-40% by weight and especially about 1-20% by weight of phospholipid or mixture is employed, based on the aqueous phase. Suitable mixtures contain approximately up to about 60% by weight of cholesterol and up to about 15% by weight of charge carrier. Solvents used for the phospholipids or mixtures are preferably methanol, ethanol, isopropanol, diethyl ether, dioxane, acetone, chloroform, acetonitrile, dimethyl sulfoxide and mixtures of these solvents.

Current US Original Classification (1):
424/450

CLAIMS:

9. An aqueous dispersion according to claim 6, wherein said dispersion contains 0.1-40 wt % phospholipid or phospholipid mixture based on the total aqueous phase.

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L3: Entry 92 of 116 File: USPT Jul 9, 1996

DOCUMENT-IDENTIFIER: US 5534241 A
TITLE: Amphipathic polychelating compounds and methods of use

Abstract Text (1):
An amphipathic polychelating compound including a hydrophilic polymeric moiety having a main backbone and a plurality of reactive side groups, a lipid-soluble anchor linked to the N terminal of the polymeric moiety, and a plurality of chelating agents linked to the side groups of the polymeric moiety. The polychelating compounds are bound to liposomes or micelles for use as diagnostic and therapeutic agents.

Brief Summary Text (2):
This invention relates to amphipathic polychelating compounds for use in liposomes or micelles.

Brief Summary Text (9):
The lipid-soluble anchor can be a phospholipid, e.g., phosphatidyl ethanolamine, phosphatidyl inositol, glycolipid, long-chain fatty acid, cholesterol, a long-chain, polar, lipid-soluble molecule having more than 5 carbon atoms in the chain, stearylamine, or reactive derivative thereof.

Brief Summary Text (15):
Lipid membrane components are any lipid-soluble molecules that can form a lipid bilayer membrane or a micelle including, e.g., phospholipids, glycolipids, cholesterol, and derivatives thereof.

Detailed Description Text (39):
The lipid-soluble anchor can be any water-insoluble, polar, lipid-soluble molecule that is easily miscible with components of natural or synthetic lipid bilayer membranes or lipid micelle monolayers, e.g., phospholipids, phosphoglycerides, and glycolipids. For example, the lipid-soluble anchor may be a phospholipid, e.g., phosphatidyl ethanolamine (PE), or phosphatidyl inositol (PI), a glycolipid, e.g., a ganglioside, cholesterol and its derivatives, e.g., cholesteryl chlorocarbonate, or a long-chain saturated or unsaturated fatty acid or other long-chain, polar, lipid-soluble molecule, having at least 5, and preferably at least 10, carbon atoms, e.g., palmitic, stearic, myristic, or oleic acids, and derivatives thereof.

Detailed Description Text (86):
Upon incorporation into the lipid bilayer of a liposome, or the lipid monolayer of micelles, the polymeric moiety of the polychelating compound forms a "coat" of numerous chelated metal or paramagnetic ions on the surface of the liposome or micelle, which are available for contact with exterior water environment.

Detailed Description Text (101):
The liposomes or micelles containing the amphipathic polychelating compounds can be further modified to alter the natural targeting of liposomes for the macrophage-monocyte system, e.g., liver, spleen, bone marrow, and lymph nodes. For example, liposomes can be modified with a surface-bound targeting group, such as an antibody, to target a particular organ or tissue within the body. Moreover, the liposomes can be modified to include protective polymers to reduce the normal

uptake of the liposomes by the macrophage-monocyte system, to significantly increase the circulation time, or half-life, within the body.

Detailed Description Text (103):
To obtain a liposome or micelle that is targeted for a specific antigen tissue, organ, or in the body, a targeting group is bound to the lipid membrane surface of the liposome, or linked to the micelle. For example, the carbohydrate portion of the membrane is oxidized, e.g., by exposure to sodium metaperiodate to yield aldehyde groups, which are highly reactive and will bind the target group to the membrane. In addition, the target group can be linked to a lipid-soluble anchor as described above, and the anchor is then intercalated into the liposome membrane. These and other methods of binding targeting groups to liposome membranes are described in U.S. Pat. No. 4,483,929, which is incorporated herein by reference. These methods are suitable for use with liposomes containing the amphipathic polychelating compounds of the invention.

Detailed Description Text (122):
When labeled with paramagnetic ions or radioactive isotopes, the liposomes or micelles containing the polychelating compounds are superior contrast agents for MRI or radioscintigraphy, respectively, of the organs and tissues in the macrophage-monocyte system. If such labeled liposomes are additionally modified with a target group and/or other surface modification to achieve a longer circulation time, they can be used as contrast agents for a specific target in the body or for blood pool imaging.

Detailed Description Text (123):
A diagnostically effective amount of liposomes or micelles is administered to a patient, e.g., intravenously or subcutaneously, using standard techniques, to achieve a change in the signal of the target by at least 10 percent. The specific amount depends upon the potency of the labeling ion, weight of the patient, and clearance of the compound from the body.

Detailed Description Text (129):
In the case of radiotherapy, a therapeutically effective amount or dosage of liposomes or micelles is administered to a patient, e.g., intravenously or subcutaneously, using standard techniques, to achieve a certain level of radiation delivered to the target, e.g., a tumor, both in amount and distribution, without damaging surrounding healthy tissue. The specific dosage depends upon, e.g., the radioactivity of the ion, weight of the patient, and rate of targeting and clearance of the compound from the body. A dosage of about 3 to 5 times that used for imaging with radioactive isotopes, e.g., about 5 to 50 mCi, should provide effective radiotherapy.

Detailed Description Text (130):
Another therapeutic use of the polychelating compounds is for treatment of metal poisoning. For such treatments, the liposomes or micelles containing the polychelating compound are administered without any ions linked to the chelating agents, which allows the chelating agents to chelate the harmful metals in the patient's body. For example, a compound including deferoxamine as the chelating agent can be used to remove excess iron in a patient when administered intravenously in a dosage of 1 to 4 g of the deferoxamine/day. For the treatment of lead poisoning, a compound with DTPA as the chelating agent can be administered intravenously at a dosage of 0.5 to 1.0 g/day. In each case, the patient's urine metal level is monitored to determine when a sufficiently low level of the metal has been reached.

Current US Cross Reference Classification (1):
424/450

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L3: Entry 97 of 116 File: USPT Jul 19, 1994

DOCUMENT-IDENTIFIER: US 5330689 A
TITLE: Entrapment of water-insoluble compound in alpha tocopherol-based vesicles

Brief Summary Text (7):
The original method for liposome preparation [Bangham et el., J. Mol. Biol. 13:228 (1965)] involved suspending phospholipids in an organic solvent which was then evaporated to dryness, leaving a waxy deposit of phospholipid on the reaction vessel. Then an appropriate amount of aqueous phase was added, the mixture was allowed to "swell" and the resulting liposomes which consisted of multilamellar vesicles (hereinafter referred to as MLVs) were dispersed by mechanical means. The structure of the resulting membrane bilayer is such that the hydrophobic (non-polar) "tails" of the lipid orient toward the center of the bilayer, while the hydrophilic (polar) "heads" orient toward the aqueous phase. This technique provided the basis for the development of the small sonicated unilamellar vesicles (hereinafter referred to as SUVs) described by Papahadjopoulos and Miller [Biochim. Biophys. Acta. 135: 624 (1967)].

Brief Summary Text (8):
An effort to increase the encapsulation efficiency involved first forming liposome precursors or micelles, i.e., vesicles containing an aqueous phase surrounded by a monolayer of lipid molecules oriented so that the polar head groups are directed toward the aqueous phase. Liposome precursors are formed by adding the aqueous solution to be encapsulated to a solution of polar lipid in an organic solvent and sonicating. The liposome precursors are then emulsified in a second aqueous phase in the presence of excess lipid and evaporated. The resultant liposomes, consisting of an aqueous phase encapsulated by a lipid bilayer are dispersed in aqueous phase (see U.S. Pat. No. 4,224,179 issued Sep. 23, 1980 to M. Schneider).

Brief Summary Text (22):
(2) have high encapsulation efficiencies compared to phospholipid MLVs;

Detailed Description Text (12):
In complete contrast to reported methods for multilamellar vesicle formation [e.g., phospholipid vesicles or the cholesterol liposomes of Brockerhoff and Ramsammy, Biochim. Biophys. Acta. 691:227 (1982)], the method for the formation of the alpha-tocopherol multilamellar vesicles of the present invention does not require the use of organic solvents. Furthermore, unlike the method of Brockerhoff and Ramsammy sonication is not necessary to form multilamellar vesicles. Sonication of the milky suspension of the alpha-tocopherol multilamellar vesicles of the present invention, or the use of a French press (SLM-Aminco, Urbana, Ill.) followed by sonication, may be used however to convert the milky suspension of multilamellar alpha-tocopherol vesicles to a clear suspension of unilamellar vesicles. Often, use of the French press without sonication results in unilamellar vesicles.

Detailed Description Text (28):
In another example of their use, the alpha-tocopherol vesicle-entrapped compounds may be incorporated into a broad range of materials including but not limited to lipid vesicles or liposomes, gels, oils, emulsions and the like. For instance, the suspension containing the entrapped compound may be added to the aqueous phase as an ingredient in any type of liposome preparation (e.g., phospholipid SPLVs, MPVs,

FATMLVs, MLVs, SUVs, LUVs, REVs, and others). This allows the entrapment of the water-insoluble compound in the phospholipid liposomes.

Current US Cross Reference Classification (2):
424/450

Other Reference Publication (10):
Lai, et al., "Thermotropic Behavior of Aqueous Dispersions of Phosphlipid Cholestrylhemisuccinate and Phospholipid-Tocopherol hemisuccinate Mixtures", Biophysical Journal Abstracts, vol. 45, No. 2, Part 2, p. 1924, Feb. 19-23, 1984.

Other Reference Publication (13):
Massey, et al., "Interaction of Vitamin E with Saturated Phospholipid Biolayers,", 1982, Biochem. Biophys. Res. Comm., 106:3, 842-847.

Other Reference Publication (15):
Papahadjopoulos, et al., "Phospholipid Model Membranes I. Structural Characteristics of Hydrated Liquid Crystals," BBA, 135:624, 1967.

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L3: Entry 113 of 116 File: USPT Aug 7, 1990

DOCUMENT-IDENTIFIER: US 4946683 A
** See image for Certificate of Correction **
TITLE: Multiple step entrapment/loading procedure for preparing lipophilic drug-containing liposomes

Abstract Text (1):
Novel liposome-entrapped cationic, lipophilic drug compositions, e.g., anthracycline antineoplastic agent compositions, and multistep entrapment/loading procedures for preparing them are disclosed. These procedures involve forming liposomes from phospholipids, such as distearoyl phosphatidylcholine or a similar long chain fatty acid diester phospholipid, to be loaded with the drug, e.g., daunorubicin or doxorubicin, in aqueous medium in the presence of an acid, e.g., an organic acid which can be monofunctional pyranosidyl acid such as lactobionic acid, adding the drug, and then adding a base such as calcium carbonate whose cations cannot pass through the vesicles' bilayers to charge neutralize the organic acid anions in the external aqueous phase and induce the acid anions in the internal aqueous phase to become neutralized by attracting the cationic, lipophilic drug.

Brief Summary Text (2):
More particularly, this invention relates to a novel multistep entrapment/loading procedure for incorporating any cationic, lipophilic drug which can partition into a lipid bilayer, and especially an anthracycline antineoplastic agent used to treat tumorous or malignant conditions in mammals, including humans, within liposome micellar particles which have been formed as unilamellar or multilamellar lipid vesicles. This novel entrapment/loading procedure facilitates the passage of the drug from the lipid membrane into the internal aqueous space within the liposome, thereby increasing entrapment efficiency and thus the amount of the drug deliverable within the body, e.g., the amount of an antineoplastic agent deliverable to tumor tissues. In the case of antineoplastic agents, the other benefits which have come to be associated with liposome-entrapped anthracycline antineoplastic agent therapy are also provided: increased in vivo stability for the drug delivery system, increased specificity of delivery of the drug to the tumor tissue site(s), decreased cardiotoxicity, and the ability to produce, and thus administer, these drug delivery systems on a large scale.

Brief Summary Text (20):
Cationic anthracycline compounds having antineoplastic activity against cancerous tissues or cells, including daunorubicin (also known as daunomycin), doxorubicin (also known as adriamycin), aclacinomycin A, vinblastine, vincristine, mitomycin C, and the like, are particularly preferred for incorporation within liposome micellar particles using the novel multistep entrapment/loading procedure of this invention. Structurally, these anthracycline compounds contain a hydrophobic tetracycline ring system coupled to an amino sugar through a glycoside linkage.

Brief Summary Text (22):
Liposome bilayer membrane particles which have been found to be suitable in practicing this invention are small [e.g., from about 30 to about 150 nanometers (nm), and preferably from about 45 to about 60 nm, in diameter as determined, for example, using a light scattering particle sizer]neutral (uncharged or having balanced charges; i.e., zwitterions) unilamellar or multilamellar phospholipid

vesicles or liposomes tailored to maximize entrapment/loading of a cationic, lipophilic drug by the method of this invention and to induce specificity and tissue/cell targeting, thereby maximizing uptake of the resulting liposome drug delivery system.

Brief Summary Text (24):
Such liposome bilayer membrane particles include ones made from dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine, dioleoyl phosphatidylethanolamine, distearoyl phosphatidylserine, dilinoleoyl phosphatidylinositol, distearoyl phosphatidylglycerol, and the like, or mixtures thereof. Liposome bilayer membrane particles made entirely from neutral phospholipids, such as distearoyl phosphatidylcholine, and preferably ones which have been further stabilized with cholesterol or like-acting substances, for example in a molar ratio of distearoyl phosphatidylcholine: cholesterol of about 2:1, respectively, have been found to be particularly suitable with regard to targeting efficiency when used to deliver anthracycline antineoplastic agents.

Current US Cross Reference Classification (2):
424/450

CLAIMS:

1. A method of preparing a phospholipid-entrapped cationic, lipophilic drug composition which comprises:

a. forming liposomes in an aqueous medium containing an acid which has at least one ionizable functional group, is of sufficient polarity to be highly soluble in water and exhibits a low permeability through the vesicle membranes to give an acidic liposome-containing aqueous medium in which the acid is present in the internal and external liposome phases, said liposome being prepared from hydroxyamino(lower) aliphatic-substituted phosphatidyl carboxylic acid diesters of a tri- or higher functional aliphatic polyol in which the ester moieties are derived from a saturated or ethylenically unsaturated aliphatic monocarboxylic acid having at least 14 carbon atoms,

b. adding to the thus-obtained acidic liposome-containing aqueous medium a cationic, lipophilic drug, and

c. then adding a base whose cations cannot pass through the liposomes' lipid bilayers to charge neutralize the acid anions in the external aqueous phase, thereby inducing the cationic, lipophilic drug to pass into the liposomes' internal aqueous phase.

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L6: Entry 39 of 51 File: USPT Jul 25, 1995

DOCUMENT-IDENTIFIER: US 5435989 A
**** See image for Certificate of Correction ****
TITLE: Method of targeting a specific location in a body

Brief Summary Text (7):
Prior attempts to improve treatment of tumors by chemotherapeutic agents have included encapsulation of such agents within biodegradable phospholipid micellular particles in the form of vesicles or liposomes. Encapsulation is thought to reduce the potential toxicity from the circulating drugs. Researchers have also sought to utilize such encapsulation to selectively target tumors within a body for delivery of chemotherapeutics. However, until the invention disclosed in the present application and the related application Ser. No. 363,593, efforts to locate or treat tumor cells with drug-encapsulating targeting particles have not been successful.

Brief Summary Text (15):
The method of this invention includes the provision of phospholipid micellular particles such as vesicles. Pure (more than approximately 98% pure) neutral phospholipid molecules are incorporated into small (less than 2000.ANG.) micelles so that they are a component of external surface. The phospholipid molecules and/or vesicle contents may be radiolabeled to enhance the identity of the specific location and the diagnosis of the tumor at the specific location.

Brief Summary Text (17):
When phospholipid micelles are introduced into the blood stream of a patient, the micelles move to the specific locations of cancerous growth in the patient's body, which may then be identified and treated. Drugs may be included in phospholipid vesicles and such drug-bearing vesicles may then be introduced into the patient's body for targeting the tumor locations.

Current US Cross Reference Classification (1):
424/450

L6: Entry 40 of 51 File: USPT Jun 14, 1994

DOCUMENT-IDENTIFIER: US 5320906 A
TITLE: Delivery vehicles with amphiphile-associated active ingredient

Brief Summary Text (4):
Phospholipid micellar particles in the form of unilamellar or multilamellar vesicles, also known as liposomes, have been used in a number of contexts as vehicles for the solubilization and delivery of active ingredient materials. Liposomes have proven in some cases to be highly advantageous in in vivo delivery systems in terms of biological compatibility, ability to isolate and solubilize otherwise insoluble and/or toxic active ingredients and ability selectively to deliver active ingredients to specific tissues or systems of interest.

Current US Cross Reference Classification (3):
424/450

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L6: Entry 47 of 51 File: USPT Dec 26, 1989

DOCUMENT-IDENTIFIER: US 4889722 A
TITLE: Method for inhibiting post-surgical adhesion formation by the topical administration of tissue plasminogen activator

Brief Summary Text (32):
The t-PA is ordinarily administered in a sterile formulation in a pharmaceutically acceptable carrier or vehicle such as phosphate buffered saline ("PBS"), isotonic saline, purified water, an organic carrier (which may be in an aqueous solution or suspension) such as a proteoglycan, for example a glycosaminoglycan such as hyaluronic acid or a derivative thereof (such as a pharmaceutically acceptable salt or ester thereof) or a similar polysaccharide such as chitosan or a derivative thereof, a lipid, for example, a phospholipid micelle or vesicle (the lipid may simply be a mixture of a phospholipid in water), dextran, a cellulosic material, polymers such as polyacrylamide or p-dioxanone, lactide, and/or glycolide based absorbable polymers, (the polymer may be in the form of microcapsules or it may be incorporated in a salve- or ointment-like formulation or a gel or gel-like composition), or in an aqueous solution of a surface active agent such as a polyoxyethylene-polyoxypropylene block copolymer or a sorbitan fatty acid ester-polyoxyethylene ether. Sterilization of the formulation may be accomplished in the usual ways, including aseptic preparation, filtration, exposure to gamma radiation, autoclaving, and the like.

Brief Summary Text (43):
Other procedures for containing drugs in phospholipids (micelles or liposomes) are described in Sears, U.S. Pat. Nos. 4,426,330 and 4,145,410, and Sears et al., U.S. Pat. No. 4,298,594, the disclosures of which are incorporated herein by reference.

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DOCUMENT-IDENTIFIER: US 4753788 A
TITLE: Method for preparing small vesicles using microemulsification

Brief Summary Text (4):
Unilamellar phospholipid micellular particles in the form of vesicles (also known as liposomes) have received increasing attention from researchers as carriers of various substances, such as imaging agents and for diagnosis of abnormalities such as tumors in humans using animal models. In particular, it has been shown that small vesicles (less than 2000 .ANG.) may be labelled to target tumors (Proffitt, et al., J. Nucl. Med. 24(1), p. 45-50 (1983)) incorporated hereinafter by reference. Such vesicles are also useful as potential carriers of therapeutic agents for treatment of tumors. Alternatively, small vesicles are useful for in vitro immunoassays. U.S. Pat. No. 4,342,826 and D. Papahadjopoulos (Ed.) Annals N.Y. Acad. Sci., 308 (1978). Additionally, the vesicles containing imaging or therapeutic agents may be modified by incorporating various carbohydrate derivatives into the vesicle surface to increase tissue specificity of the vesicles, or by adding cholesterol to increase the stability of the vesicles. Mauk and Gamble, Anal. Bioc. 94, pg. 302-307 (1979); Mauk, et al., P.N.A.S. (U.S.A.) 77 (8), pg. 4430-4434 (1980); and Liposome Technology, Targeted Drug Delivery and Biological Interaction, Vol. III, G. Gregoriadis (Ed.), C.R.C. Press, Inc. (1984), all of which are incorporated herein by reference.

Current US Cross Reference Classification (4):
424/450